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Inflammatory bowel disease in the elderly: a review of the literature

Mariana Guimarães Adams

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Abstract:

The aging of the population makes the problematic of inflammatory bowel disease in the elderly of increasing concern. The complexity of this age group, with its comorbidities, changing physiology and functional status, risk of polypharmacy and adverse effects, presents the caring physician with unique challenges in the management of this chronic condition. Current therapeutic algorithms may not be applicable in the elderly population and require modifications that account for age. This review examines what is already known about inflammatory bowel disease in the elderly and highlights existing gaps in understanding that require further investigation as a framework for development of clinical guidelines suited to this distinctive population.

Keywords: Inflammatory bowel disease (IBD), Crohn's disease, Ulcerative colitis, elderly-onset IBD, late-onset IBD and long-standing IBD, epidemiology, pathophysiology, genetics, immunology, immunosenescence, environmental factors, gut microbiome, clinical presentation, differential diagnosis, therapy, aging.

Resumo:

O envelhecimento da população torna a problemática da doença inflamatória intestinal no paciente idoso cada vez mais relevante. A complexidade desta faixa etária, com as suas comorbilidades, alterações fisiológicas e detrimento funcional, assim como o risco acrescido de polifarmácia e iatrogenia colocam desafios acrescidos à abordagem médica desta doença crónica. Os algoritmos terapêuticos correntemente em prática frequentemente são difíceis de aplicar na população idosa sendo necessárias modificações que tomem em consideração a idade. Este artigo de revisão propõe examinar o conhecimento já existente à cerca da doença inflamatória intestinal e sublinhar áreas de compreensão que necessitam de investigação acrescida no sentido de permitir a criação de normas de orientação clínica adaptadas a esta população distinta.

Palavras chave: Doença inflamatória intestinal (DII), doença de Crohn, colite ulcerosa, DII de longa duração, DII de início tardio, DII geriátrica, epidemiologia, fisiopatologia, genética, imunologia, imunossenescência, fatores ambientais, microbioma intestinal, apresentação clínica, diagnóstico diferencial, terapia, envelhecimento.

Resumo do Trabalho:

A doença inflamatória intestinal é uma doença crónica cuja história natural determina, pela sua gravidade e duração, custos socioeconómicos consideráveis. O número de doentes com idade superior a 65 anos, portadores de DII, é cada vez maior, dado o envelhecimento da população e o aumento de incidência da doença. A DII no doente idoso afeta dois grupos populacionais diferentes. Um grupo no qual o diagnóstico foi feito na infância ou em idade adulta (i.e. DII de longa duração) e outro constituído pelos doentes com diagnóstico recente (i.e. DII geriátrica). O presente trabalho pretende sumarizar a literatura existente relativamente às características destas duas entidades, providenciar informação para a adequação da estratégia terapêutica à população idosa com DII e identificar áreas de conhecimento que necessitem de mais investigação.

A evidência, relativamente às diferenças entre DII de longa duração e geriátrica, é contraditória, havendo estudos que indicam fenótipos díspares e outros que apontam para características similares. No entanto, é importante considerar que o doente idoso é complexo em si mesmo, não apenas pelas comorbilidades de que padece, mas também pela polifarmácia inerente à sua condição de fragilidade. Assim sendo, quaisquer interpretações sobre a gravidade de doença ou suas manifestações sintomáticas têm de ser contextualizadas face ao doente em questão. A evidência parece apontar para uma menor severidade da DII geriátrica, com menor gravidade sintomática, ausência de história familiar e diferente localização no trato gastrointestinal, comparativamente à DII de longa duração.

O diagnóstico diferencial é dificultado no doente idoso não só pelos sintomas frequentemente indolentes e inespecíficos da DII geriátrica, mas também pelo facto de o leque de doenças a considerar nesta faixa etária ser considerável, incluindo desde a doença diverticular, a colite isquémica, a colite microscópica, a colite por anti-inflamatórios não-esteróides e doença maligna. A dificuldade do diagnóstico diferencial é assim uma importante razão para o atraso no diagnóstico de DII no doente idoso, o qual pode ir até seis anos, comparativamente ao doente jovem.

O idoso com DII tem um risco acrescido de desenvolver vários tipos de cancro e consequentemente necessita de vigilância regular e de um rastreio completo antes de iniciar qualquer terapia imunossupressora. Nos doentes com DII, o cancro colo-retal (CCR) surge em idades mais jovens do que na população geral. Consideram-se como fatores de risco para CCR nos doentes com DII o sexo masculino, a idade de diagnóstico mais jovem e a colite extensa.

Para além do risco inerente à patofisiologia da doença em si, os fármacos utilizados no tratamento da DII, nomeadamente os imunomoduladores e os agentes biológicos, estão também associados a um aumento de risco de cancro. Foram reportados casos de carcinoma do trato urinário e da tiróide com o uso de imunomoduladores como as tiopurinas, assim como um aumento do número de casos de cancro da pele não-melanoma. O tratamento dos doentes com DII que concomitantemente apresentam uma neoplasia é complexo, dado o risco de proliferação tumoral associado ao uso da medicação imunossupressora. O consenso atual nestas circunstâncias envolve a cessação das tiopurinas, dos inibidores da calcineurina e dos agentes anti-TNF alfa até o tratamento oncológico terminar. Crises ligeiras de DII podem ser tratadas com 5-aminosalicilatos e ou corticosteroides locais. O metotrexato, os agentes anti-TNF alfa e os corticosteróides sistémicos de curta duração devem ser utilizados em crises mais graves.

Na população de idosos, com idade superior a 65 anos, 20% sofre de pelo menos cinco doenças crónicas. A imunosenescência, que corresponde à diminuição da função imunológica com a idade, contribui para uma menor vigilância antitumoral, um aumento da suscetibilidade infeciosa e uma redução da resposta à vacinação. Estes factores, inerentes à idade geriátrica, contribuem para a diminuição da *performance status* do idoso e perpetuam um estado de fragilidade, que se reveste de particular relevância no doente com doença intestinal inflamatória. Idosos com DII sofrem mais frequentemente de doença cardiovascular, doença pulmonar e de diabetes *mellitus*. Uma implicação direta deste contexto geriátrico é a polifarmácia e a iatrogenia, com consequências em termos de morbilidade e mortalidade.

Quando hospitalizados, os doentes idosos com DII têm uma mortalidade superior à dos doentes mais jovens, mesmo após ajustamento para as comorbilidades e presença de complicações, demonstrando que a idade é um fator de risco independente de mortalidade. Em termos de resultados cirúrgicos, os doentes com idade superior a 60 anos têm tempo de internamento mais prolongado, com complicações acrescidas. Estas observações demonstram a complexidade do doente idoso, sendo necessário uma adaptação dos regimes terapêuticos a este grupo etário, para prevenir os internamentos, uma vigilância acrescida para evitar as complicações e a necessidade de cirurgia.

A decisão terapêutica no idoso com DII é complexa e influenciada por múltiplas variáveis associadas ao processo de senescência. Nesta faixa etária surge uma diminuição da função imunitária designada de imunosenescência, com desequilíbrios das respostas Th1 e Th2 e aumento do risco de infeção e doença maligna. A nível fisiológico, enquanto a composição

corporal em água, massa magra e volume extracelular diminui, a massa gorda aumenta, alterando o volume de distribuição de vários fármacos com implicações em termos de índice terapêutico. Por outro lado, a diminuição da taxa de filtração glomerular assim como a redução do fluxo sanguíneo esplâncnico e hepático, afetam a depuração dos fármacos. Por todos estes motivos, os regimes terapêuticos convencionais devem ser ajustados face à realidade do doente idoso, dando primazia à estratégia "*start low and go slow*".

As comorbilidades neste grupo etário frequentemente condicionam a prescrição. Um exemplo pertinente é o risco de hiperglicemia nos doentes diabéticos com a utilização de corticosteróides. Esta classe terapêutica é conhecida pelo seu perfil de efeitos secundários, o que no doente idoso tem particular relevância, nomeadamente dislipidémia, hipertensão, osteoporose, depressão e risco infecioso.

Nesta faixa etária as múltiplas comorbilidades e a polifarmácia associada representam um risco acrescido de interações medicamentosas sendo assim essencial a revisão minuciosa de toda a medicações do doente de forma a evitar reações adversas.

Perante a realidade exposta, os objetivos terapêuticos no doente idoso terão necessariamente de ser diferentes. O controlo sintomático através de um regime tolerado pelo doente, a simplificação da medicação tendo em conta as interações medicamentosas e os custos contribuem para melhorar a *compliance* e os resultados terapêuticos. Os aspetos da qualidade de vida do doente devem também ser abordados, não negligenciando sintomas como a incontinência, a disfunção sexual e a fadiga.

Os padrões de prescrição nos doentes com DII variam consoante a idade. A sulfassalazina e os corticosteróides são os fármacos mais prescritos nos idosos. Os biológicos e os imunomoduladores são significativamente menos, contrariamente ao que acontece nos doentes jovens. A aparente menor gravidade da DII geriátrica, assim como o receio de maiores efeitos adversos, poderá justificar a baixa utilização de potentes fármacos imunossupressores neste grupo etário.

O tratamento adequado da DII depende de fatores como a severidade da doença, a sua localização, a sua extensão, a resposta a tratamentos prévios, as comorbilidades e *compliance* do doente. A gravidade da colite ulderosa (CU) é avaliada pelos critérios modificados de Truelove e Witts e dividida em ligeira, moderada a grave. A doença de Crohn por sua vez é

classificada de acordo com os critérios de Montreal em termos de distribuição e em termos de gravidade pelo índice de actividade da doença de Crohn (CDAI).

Os 5-aminosalicilatos são considerados seguros e eficazes no tratamento de colite ulcerosa ligeira (CU) a moderada em doentes com DII independentemente da idade. Estes agentes não têm utilidade comprovada no tratamento da Doença de Crohn (DC).

Os corticosteroides, ao contrário do que acontece em doentes mais jovens, são usados na população idosa com DII não apenas para a indução de resposta, mas também no tratamento de manutenção, apesar das suas conhecidas complicações. O tratamento continuado com esta classe terapêutica sem um plano de redução progressiva e eventual cessação pode levar a um aumento de mortalidade destes doentes. Torna-se, portanto, crucial a existência de um follow-up periódico com revisão terapêutica em cada sessão. Atualmente, o uso desta classe farmacológica está indicado na indução de remissão da DC ligeira (com budenosido oral), moderada e grave (com corticosteroides sistémicos). Na CU, corticoides sistémicos são apropriados em doentes com doença moderada a severa ou com doença ligeira que não respondem aos 5-aminosalicilatos.

A azatioprina, a 6-mercaptopurina, a ciclosporina e o metotrexato são os quatro imunomoduladores mais frequentemente utilizados na DII. De um modo geral, não existem diferenças em termos de eficácia e toxicidade entre doentes jovens e idosos. São eficazes no tratamento de manutenção da CU ligeira a moderada refratária aos 5-aminosalicilatos assim como em doentes dependentes de corticosteroides. A ciclosporina é útil também no tratamento da CU ativa e refratária aos corticosteroides sistémicos. Na DC ativa, os imunomoduladores (exceto a ciclosporina) podem ser utilizados como complemento à terapêutica ou como agentes poupadores de corticosteroides. Esta classe farmacológica é essencial na manutenção da remissão na DC, seja localizada ou extensa, ou dependente de corticosteroides.

Os agentes anti-TNF alfa, também designados de agentes biológicos, são empregues na doença de Crohn e colite ulcerosa moderada a grave tanto na fase de indução de resposta como na fase de manutenção terapêutica. Estudos recentes demonstram que o uso precoce destes fármacos, tem a capacidade de alterar a história natural da doença a curto e a longo prazo, conduzindo à cura histológica. Estes dados contribuiram para a atual mudança de estratégia terapêutica no sentido *top-down*, ou seja, iniciar com fármacos mais agressivos e reduzir de intensidade consoante os resultados obtidos.

A abordagem *top-down*, frequente em doentes jovens, é pouco empregue em idosos não apenas por apreensão do perfil de efeitos adversos mas também porque o objetivo de cura da mucosa, um dos pilares do tratamento dos jovens, não é essencial no idoso. Assim, recomenda-se que a prescrição de biológicos em doentes idosos com DII seja adaptada à sua situação clínica, considerando o perfil de risco benefício e colocando a tónica no controlo sintomático.

Doentes com DII ativa e que manifestem intolerância ou ausência de resposta aos immunosupressores e/ou agentes biológicos existentes estão limitados em termos de opções terapêuticas. Nestes casos, e exclusivamente para a colite ulcerosa, desenvolveu-se uma técnica de leucoforese designada de aferese selectiva de granulócitos e monócitos que tem demonstrado benefício clínico e um perfil de segurança aceitável. No entanto, são necessários estudos controlados e randomizados que clarifiquem a sua eficácia na CU geriátrica e assegurem a sua segurança nesta faixa etária.

O tratamento cirúrgico está reservado para casos em que há falência da terapêutica médica ou perante complicações como a obstrução, fistulização, formação de abcessos, megacólon tóxico ou hemorragia.

O aumento da incidência da DII a nível mundial assim como as limitadas opções terapêuticas existentes presentemente reforçam a importância da investigação nesta área. O estudo do microbioma intestinal e de como a sua desregulação pode desencadear a DII num indivíduo geneticamente predisposto e a análise molecular de proteínas imunoreguladoras presentes no trato digestivo, tais como as reguladoras da sinalização de proteínas G (RGS), são dois exemplos de campos de pesquisa com vista a identificar novos alvos terapêuticos.

A DII é uma patologia crónica complexa dependente de factores genéticos, imunológicos e ambientais que requer uma abordagem especializada e multidisciplinar. Por outro lado, o doente idoso possui características específicas e uma fragilidade intrínseca, pelo que, na DII geriátrica, é de redobrada importância a necessidade de algoritmos de tratamento ao mesmo tempo adaptados e holísticos.

Só a colaboração entre a rede de saúde primária, os médicos especialistas, o doente e a sua família permitirá otimizar a eficácia do tratamento e assegurar uma melhoria na qualidade de vida do doente idoso com DII.

Do presente trabalho depreendemos que os estudos que suportam o conhecimento sobre a DII e o seu tratamento têm no geral um baixo nível de evidência científica. Numa subpopulação

com características especiais como a geriátrica, que frequentemente é excluída dos ensaios clínicos, a falta de evidência torna-se ainda mais evidente, o que dificulta bastante a decisão terapêutica neste grupo.

Concluímos que a investigação nesta área deve ser aprofundada. Necessita um esforço internacional multicêntrico no sentido de os estudos efectuados serem de elevado nível de evidência científica e de os idosos estarem adequadamente representados nos ensaios clínicos, para que as conclusões sejam válidas e transponíveis para este grupo particular. Só nestas condições será possível a criação de normas de orientação apropriadas ao doente idoso.

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Introduction:

Inflammatory bowel disease (IBD) is a chronic, progressive disease of unknown aetiology characterized by a dysregulated immune response to host intestinal flora in genetically predisposed individuals.

Statistics from the 2014 Portuguese population census demonstrate that the population over 65 years of age is increasing rapidly. In merely five years this value rose from 18.3% to 20.3%, making the Portuguese population one of the oldest in Europe [1]. The significance of this demographic pattern is made obvious when one considers consumption of health resources and associated costs.

The epidemiological transition model [2] shows that chronic conditions, a category in which inflammatory bowel disease (IBD) inserts itself, make up the larger share of the disease burden in developed countries [3]. Considering that these chronic conditions are more common in the elderly, and that they tend to coexist in this group it becomes clear that the optimization of care for such conditions is essential to reduce frailty and hence decrease acute care spending with the geriatric patient with IBD [4].

IBD in the older population can be divided into two groups: one where the disease was diagnosed in an individual at a late age (late-onset IBD) and another so called long-standing IBD, where the diagnosis was made at a younger age [5].

The definition of elderly IBD patients remains far from clear with ranges from 40 to 75 years old mentioned in the literature. Recent publications have employed the >60 and >65 cut-offs as defining of elderly-onset IBD but a consensus is lacking [5] [6] [7] .

Approximately 10-15% of IBD cases are late-onset IBD diagnosed in people over the age of 60 [6] [8]. Since IBD has a negligible impact on mortality, the pool of IBD patients over the age of 60 will be significant as we add the late-onset and the surviving long-standing IBD subgroups. There are considerable challenges to the management of elderly patients with IBD. These patients are commonly fragile, with multiple comorbidities that can not only delay and confound the diagnosis of IBD but also aggravate the course or complicate treatment of the disease.

Information for this review was obtained through searches on PubMed using the following keywords: inflammatory bowel disease (IBD), Crohn's disease, Ulcerative colitis, elderly-onset IBD, late-onset IBD and long-standing IBD, epidemiology, pathophysiology, genetics, immunology, immunosenescence, environmental factors, gut microbiome, clinical presentation, differential diagnosis, therapy, aging. The review included editorials, case studies, narrative reviews, systematic reviews, meta-analyses and randomized controlled trials, from 1980 to the present year.

This review is intended to summarize the available literature relative to the differences and similarities between late-onset and long-standing IBD in terms of epidemiology, clinical presentation, prognosis and treatment as well as point out areas of knowledge where further investigation is need. The goal is to inform physicians and thereby allow them to tailor therapeutic strategies to the elderly IBD population under their care.

Epidemiology:

It has been proposed that IBD follows a bimodal incidence pattern, with an incidence peak at a younger age and a second incidence peak later in life [9] [10] [11] [12] [13]. However, this pattern is far from consensual and several epidemiological studies have failed to demonstrate it since Loftus et al. 1998 [14] first questioned this data [8] [15] [16] [17] [18]. This discrepancy might have arisen because the initial studies demonstrating a bimodal distribution utilized more rudimentary diagnostic criteria for IBD, based on clinical observation or X-ray findings, with colonoscopy as an option not a mandate. Also, these studies were held in reference centres for the disease where the likelihood of selection bias is greater.

With the aging of the present IBD patient population added to the patients who are diagnosed at a later stage, the number of elderly patients with IBD is on the rise. Allied to the fact that incidence of IBD appears to be increasing [19], clinicians will need to be prepared to handle increasingly complex geriatric patients.

Currently, the global burden of IBD represents 0.5% of the general population. In Europe, there are approximately 2.5-3 million people diagnosed with this condition and the associated health costs are estimated to be € 4.6–5.6 billion annually [19]. Azevedo L.F (2010) developed a pharmacological approach to estimate the prevalence of IBD in Portugal where intestinal anti-inflammatory drug (IAI) consumption as well as mean prescribed daily dose were analysed. Per this study, the prevalence of IBD in Portugal increased from 86 to 143 per 100,000 between 2003 and 2007. UC prevalence rose from 42 to 71 and CD from 43 to 73 per 100,000 [20].

Incidence figures for late-onset IBD lie somewhere in the interval of 10-15% of all IBD patients. [5]. A large population-based cohort study by Charpentier et al, 2014 determined that 5% of Crohn's disease (CD) and 11% of ulcerative colitis (UC) diagnoses were made in individuals aged over the age of 60 [6]. This same study demonstrated that among the IBD population studied, the proportion of CD was lower in the elderly-onset patients than in younger adults while the proportion of UC was higher.

In Portugal, epidemiological data on elderly onset IBD are scarce and considering the Southern-European regional differences in IBD incidence rates [21], mere extrapolation data may prove an inaccurate approach. Therefore, further studies are required to provide this incidence data as well as a phenotypic description of this subset of IBD as applies to this European country.

Clinical Presentation:

Evidence regarding the clinical features of IBD in the elderly onset population is conflicting. Some studies state that late onset IBD has certain phenotypic characteristics that differ from long standing IBD in terms of severity, disease location and presenting symptoms [6] [22] while others state that there is a general similarity of features between these two groups [5]. The argument as to whether elderly-onset and long-standing IBD are in fact two genotypically different disorders, with their respective phenotype, is still unresolved [23].

A milder course has been suggested [24] for the elderly onset patients, with lower utilization of immunosuppressants [25] and lower cumulative probability of surgery at 5 years in this group [6]. However, some authors suggest that the initial flare is more severe in the elderly-onset IBD subgroup [26].

A point to consider when analysing seemingly conflicting results in disease severity is that the elderly patient is complex and therefore despite a milder disease course, disease flares can be conducive to higher rates of hospitalization, morbidity and mortality simply due to comorbidities that these patients possess [27]. Also, older-onset IBD is associated with increased rates of misdiagnosis owing to the wide range of differential diagnosis that must be considered in this age group, which contributes to a delayed diagnosis [7] and hence poorer outcomes.

A large population-based cohort study by Charpentier et al presented data on the natural history of elderly-onset IBD. Regarding CD the study determined that elderly onset CD phenotype is more often inflammatory and rarely progresses to the stricturing or fistulizing behaviour. It´s location is commonly colonic or ileocolonic and as such symptoms of rectal bleeding and anal fistulas are less frequently reported [6].

Elderly onset UC presents more often as left-sided or extensive disease and disease location tends to remain stable over time. Symptoms of rectal bleeding and abdominal pain are less common in the elderly cohort [6]. A family history is uncommon in both CD and UC of elderly onset, which points towards a larger influence of environmental factors in the disease aetiology over the genetic or immunological influence [28].

Most studies demonstrate that the risk of extra-intestinal manifestations is similar between the elderly-onset and long-standing IBD populations [26] [29]. In patients over 60, approximately 13% will develop an extraintestinal manifestations. The most common of these manifestations

is arthritis, followed by uveitis, spondylitis and erythema nodosum [15]. Arthritis in IBD is classified as a seronegative spondyloarthropathy, associated with a positive HLA-B27 genotype and occurs in up to 30% of IBD patients [30]. It is often divided into two categories, peripheral and axial arthritis, according to the joints involved. Peripheral arthritis can be subdivided into type I, a pauci/oligoarticular arthritis particularly affecting the larger joints of the lower extremities, and type II, a polyarticular arthritis of symmetrical distribution and affecting the upper limbs predominantly [31]. The axial pattern of distribution includes sacroiliitis, inflammatory back pain (IBP) and ankylosing spondylitis. Type I peripheral arthritis is acute in onset, correlates with IBD activity and tends to improve upon commencement of IBD-directed therapy. Type II peripheral arthritis and axial arthritis are independent of disease activity require specific treatment other than that initiated for IBD. NSAID's, corticosteroids and analgesics are the three most commonly prescribed drug classes for the management of IBD arthritis. NSAID's are particularly nefarious in the elderly patient. Pharmacokinetic and pharmacodynamic changes that occur in this age group increase the sensitivity of the patient to this drug class and lead to increased risk of cardiovascular, neurological, renal and hepatic side effects [32]. Therefore, prescribing for an elderly IBD patient must take into consideration the risk vs benefit ratio of each drug class employed.

The following table shows the main clinical presentation differences between elderly-onset and long-standing IBD [6] [5].

Table 1: Features of elderly-onset vs long-standing IBD. ***Note:*** **adapted from** ***Gisbert and Chaparro, Systematic review with meta-analysis: inflammatory bowel disease in the elderly, 2013, Table 2*** **and** ***Charpentier et al, Natural history of elderly onset inflammatory bowel disease: a population-based cohort study, 2013, Table 1 and 2*****.**

Characteristic	Elderly Onset IBD	Long-standing IBD
Age at diagnosis	>60 years of age, though there is no consensus as to the cut off age. This population accounts for 10-15% of all IBD cases.	2nd to 4th decades of life is the most common age bracket at diagnosis, though paediatric cases account for 10% of all IBD cases
Presenting symptoms	**CD:** less diarrhoea, abdominal pain and fever, but more rectal bleeding and anal fistula	**CD:** weight loss, fever, abdominal pain and diarrhoea are common
	UC: less rectal bleeding and abdominal pain. More severe initial attack.	**UC:** weight loss, rectal bleeding and abdominal pain. Usually less severe initial attack.
Family history	Uncommon	Frequently present
Location	**CD:** colonic localization is more common. Disease location tends to remains stable.	**CD:** ileo-colonic involvement, disease progression common.
	UC: mainly left-sided at diagnosis.	**UC:** left-sided or extensive disease at diagnosis. Proctitis is more common in this group.
Clinical course	**CD:** inflammatory behaviour is more common at diagnosis, with a less aggressive disease course.	**CD:** more aggressive, with structuring and fistulising behaviours developing commonly
	UC: more favourable clinical course with less proximal extension over time	**UC:** more aggressive, with greater proximal progression over time.

Differential diagnosis:

IBD are frequently non-specific and allow for multiple diagnoses to be considered. The situation is further complicated should the patient in question be an elderly individual, in which conditions that mimic IBD are more common [7]. In the elderly-onset IBD subgroup, presenting symptoms are often indolent and atypical, with less abdominal pain, bleeding, systemic symptoms and extra-intestinal manifestation compared to younger IBD patients. All these factors contribute to a delay in diagnosis of up to 6 years in older patients compared to 2 years in younger patients, with initial misdiagnosis rates of 60% compared to 15% in younger patients [33].

The differential diagnosis of IBD is complicated in the elderly individual, in which conditions such as complicated diverticular disease, ischaemic colitis, infectious diarrhoea, microscopic colitis, NSAID colitis and colorectal cancer, that can mimic IBD, are more common [7].

Complicated diverticular disease can present with localized abdominal pain, rectal bleeding and diarrhoea, symptoms which overlap those of IBD. Diverticular disease may coexist with IBD and can also mimic CD of the colon, particularly in cases of fistulisation and perforation. Of particular interest is the so called segmental colitis associated with diverticular disease (SCAD), which can resemble IBD clinically, endoscopically and histologically [34].

Ischaemic colitis is a large spectrum disease ranging from transient and self-limited mucosal and/or submucosal ischaemia to an acute, transmural infarction that may evolve to necrosis and death. It presents with abrupt onset of abdominal pain over the affected segment and stool mixed with blood. It most commonly affects elderly patients and due to its potential gravity, it must always be ruled out before pursing investigations for IBD [24].

Infectious colitis is an important diagnosis in the elderly population, not only due to the so-called immunosenescence phenomenon [35] but also due to changes in the gut microbiota that occur in this age group [36]. It can be taken for IBD, especially UC and must be included in the differential diagnosis of patients with diarrhoea. Pathogens such as *Campylobacter, Clostridium difficile, Eschericha coli O157:H7, Giardia lamblia, Histoplasma, Mycobacterium tuberculosis, Salmonella* and *Shigella* can present similarly to IBD [37]. Of note, Salmonella and E. coli O157:H7 can both present with a more severe course in elderly patients and therefore require antibiotics considerably more often than their younger counterparts [38].

Clostridium difficile infection (CDI) has an increased incidence in IBD patients, particularly those on corticosteroids and immunomodulators [39]. On the other hand, as part of the immunosenescence process, the microbiome of the elderly patient is altered with increasing numbers of atypical *Bacteroides* and *Clostridia* species [40], facilitating the appearance of Clostridium difficile associated disease (CDAD). CDAD is much more severe in a patient with IBD [41], with increased rates of hospitalization and colectomy compared to non-IBD patients [42]. Therefore, CDI testing should be considered on all IBD patients with a disease flare and/or who are not responding to treatment.

Microscopic colitis (MC) is an inflammatory disease of the bowel where patients present with chronic watery diarrhoea. Though appearing grossly normal on colonoscopy, histological analysis of the mucosa reveals two subsets of disease: collagenous colitis or lymphocytic colitis. The incidence of MC increases greatly with age [43] must be considered in the differential diagnosis of elderly-onset IBD.

NSAID colitis is an intestinal inflammation secondary to NSAID intake, presenting with a wide variety of symptoms, from GI bleeding to abdominal pain, gastroduodenal ulceration and perforation that can mimic IBD. NSAID can not only precipitate flares of UC and CD but also this drug class is often required in IBD patients for the treatment of other comorbidities or for pain relief from axial IBD arthritis and hence ceasing it is not always simple. Therefore, a thorough review of the patient's regular medications is essential and a trial of cessation can be employed where doubt remains as to the cause of the symptoms.

Cancer and IBD:

Elderly IBD patients are at an increased risk of developing several types of cancer when compared to the general population [44] and therefore warrant close surveillance and a full screening before starting any immunosuppressant therapy [45].

Though past data regarding the risk of colorectal cancer (CRC) in IBD patients was conflicting, recent meta-analyses have clarified that there is in fact an increased risk in this population [46] [47]. The risk for developing CRC appears larger in UC, with a standardized incidence ratio of 2.4 compared to 1.9 for CD [46] [47]. Male sex, younger age at diagnosis and extensive colitis were determined to be significant risk factors [47]. CRC diagnosis is made at a younger age in IBD patients but there has been no consistent demonstration of increased mortality in the IBD population group [47].

A recent population-based study by Cheddani et al demonstrated that there is no increased risk of CRC in elderly-onset IBD patient within the 6-year follow-up window of the study [48]. Therefore, further studies with longer follow-up times are required to validate these results. Current ECCO Consensus Statements on Inflammatory Bowel Disease and Malignancies recommend endoscopic surveillance tailored to the patient's risk profile [45]. Risk factors to consider include duration of disease, extension, severity, presence of primary sclerosing cholangitis and family history of CRC. Of note, the extent of inflammation of the colon is the best established risk factor, such that CRC risk is highest in pancolitis [49].

Drugs commonly used in the treatment of IBD have been associated with increased risk of malignancy, namely immunomodulators and biologics. The use of these medications in the setting of chronic inflammation (which characterizes IBD) generates concerns regarding their contribution to increased risk of IBD-related cancers [50].

There are reports of thiopurine-related urinary tract [51] and thyroid cancers as well as melanoma in IBD patients [50]. Also, thiopurine use and increasing age have both been linked to increased rates of non-melanoma skin cancers (NMSC) [52].

Furthermore, thiopurine exposure was associated with a three- to fivefold increased risk of lymphoma [53], particularly in older IBD patients. These thiopurine-associated lymphomas are typically caused by the reactivation of a hereto latent Epstein Barr virus (EBV) infection [54]. Anti-TNF agents infliximab and adalimumab have also been linked to increased risk of malignancy, namely melanoma and lymphoma [55] [7]. However, several case-control and

cohort studies have suggested that these agents in monotherapy do not increase the risk of cancer in IBD patients [45]. All in all, the evidence available seems to suggest no increased long-term cancer risk of anti-TNF agents in IBD patients [56].

Apart from medication there are other IBD-specific factors such as early disease onset, male gender and age > 65 which also contribute to increased risk of malignancy, particularly haematological cancers and that must be considered when analysing the patient's risk profile [45].

Management of IBD patients with a history of cancer can be difficult. Immunosuppression has been associated with increased recurrence of cancer [57] and therefore controlling active IBD with immunomodulators can prove problematic. Biologicals remain unclear in terms of safety in IBD cancer patients, not only in terms of risk of tumour growth but also in terms of pharmacological interactions, especially in elderly individuals who are often excluded from clinical trials pertaining to this drug class [25] [58]. The ECCO Consensus Statements suggest multidisciplinary management of IBD cancer patients and cessation of thiopurines, calcineurin inhibitors and anti-TNF agents until cancer therapy is completed. IBD flares in patients with a history of cancer can be managed with 5-aminosalicylates and/or local corticosteroids. More severe flares can be addressed with methotrexate, anti-TNF and short-term systemic corticosteroids [45].

Morbidity and Mortality:

The elderly are increasingly prone to comorbidities such that 20% of patients aged ≥65 years have at least 5 chronic conditions [59]. This reality not only undermines their performance status but also helps to perpetuate a state of frailty. A recent retrospective observational study has reported that elderly IBD patients suffer most commonly from cardiovascular or pulmonary disease as well as diabetes mellitus. Among the geriatric IBD patients, 33.8% had coronary artery disease (CAD), 22.6% with chronic lung disease, 22.6% with congestive heart failure and 18.8% with diabetes mellitus [60]. A direct implication of this fact relates to the risk of polypharmacy and the iatrogenic effects derived therefrom. This same study went on to determine that the average number of medications taken on a regular basis by an elderly IBD patient was 7 ± 3.5 and that 21% of this patient population had major polypharmacy. A known consequence of polypharmacy is prescribing cascades where, to relieve symptoms that are in fact due to adverse drug interactions, a new agent is commenced. To avoid this, constant update of medication sheets is needed, with removal of all unnecessary agents and simplification of drug regiments [35].

Older patients with IBD are in themselves a high-risk group. When hospitalized they have a higher mortality rate than younger patients, even after adjusting for comorbidities and the presence of complications [61] . Age therefore appears to be an independent risk factor for adverse events in IBD [62]. If further studies come to validate this finding, the creation of guidelines specific for elderly IBD patients becomes even more relevant in an attempt to reduce mortality by targeting age as a risk factor.

Geriatric IBD patients also demonstrated increased incidence of thromboembolic events, with hypercoagulability and subsequent thrombosis complicating 3% of all IBD-related admissions [63, 64]. However, overall mortality of UC patients is not higher than that of the general population and in CD, its effect on mortality remains controversial.

In terms of surgical outcomes, older patients had a longer post-operative stay than younger patients which might suggest increased incidence of complications, especially cardiovascular and pulmonary [65] [27]. Interestingly, older patients were less likely to undergo surgery and therefore one must consider whether comorbidity and the presence of complications may be preventing these patients from being good surgical candidates [61]. Exceptions to this were

older patients presenting with fistulising or stricturing disease who were more likely to proceed to surgery than younger cohorts. These disease phenotypes may be less tolerated in the elderly and therefore not amenable to conservative medical management.

Treatment considerations:

Age associated variables that influence the management of IBD:

Polypharmacy and potential medical interactions:

As previously stated, the medical management of IBD in the elderly is often complicated by comorbidities that generally imply complex drug regiments and increased risk of pharmacological interactions. The state of being elderly is in itself a risk for these adverse effects due to changes in physiology which significantly affect pharmacokinetics and pharmacodynamics. As body fat increases and total body water, extracellular volume and lean muscle mass decrease, distribution volumes of both hydrophilic and lipophilic drugs are affected and hence require adjustment [35] [66]. Drug clearance is affected not only by reduced glomerular filtration rates but also reduced splanchnic and hepatic vascular flows that occur with aging [67]. Also to bear in mind are the age-associated changes in circulating plasma proteins that inherently influence the levels of protein-bound drugs. Therefore, conventional dosing regiments will mostly likely require age-based adjustments and prescribing should follow the "start low and go slow" approach [5].

Nutritional deficiencies:

Elderly patients with IBD are frequently deficient in vitamin B12, vitamin D and iron [68]. In elderly-onset CD, increased disease duration was correlated with the presence of the above mentioned nutritional deficiencies but no such correlation was found for geriatric UC [60]. Elderly patients with IBD are commonly protein deficient, with protein energy malnutrition (PEM) occurring in 20-85% of these patients [68]. These findings reinforce the importance of repeated nutritional assessments, especially in patients with longer duration of IBD.

Comorbidity:

Pre-existing comorbidities may influence medication regiments used to treat an elderly patient's IBD. For example, the use of corticosteroids in diabetic patients may be limited by the risk of developing hyperglycaemia, hyperlipidaemia and hypertension. Besides the risk of serious infection, other adverse effects of chronic corticosteroid use include cataracts, glaucoma, depression and osteoporosis [66]. Also noteworthy is the recommendation to avoid anti-TNF agents in patients with class III and IV congestive heart failure and central demyelinating diseases [69]. Infliximab for instance interacts with sulfonylureas, simvastatin,

and pain medication such as tramadol and fentanyl, agents prescribed for common comorbidities such as hypercholesterolemia, pain and diabetes [66]. These are but three examples that signal the need for coordination of care across medical specialties and personalization of drug regiments to the patient at hand.

Immunosenescence:

Aging is associated with decreased immune function in a process called immunosenescence. There is thymic atrophy with decreased T cell production and functionality. Primary lymphopoiesis is reduced as evidenced by decreased T and B cell bone marrow progenitors. Imbalances between Th1 and Th2 responses as well as reduced naïve T cell populations lead to increased risk of viral infection and malignant disease [70]. Decreased bone marrow production of B cell clones and antibody-forming cells has many effects ranging from decreased tumour immunosurveillance to increased susceptibility to infection and reduced response to vaccines. A theory correlating B cell immunosenescence to elderly-onset IBD suggests that, because antibody production at the level of the intestinal mucosa is important in maintaining barrier function and regulating bacterial flora, age-associated impairment of antibody production could contribute to IBD development [23]. However, no direct evidence of the link between B cell immunosenesce and IBD is yet available. The innate immune system is also affected by the aging process [71]. Neutrophils have reduced superoxide production and their capacity for phagocytosis is reduced [72]. Dendritic cells suffer changes related to their maturation, with decreased threshold of activation, altered profile of cytokine secretion and decreased antigen uptake. Macrophages have reduced phagocytic capacity and secrete larger amounts of pro-inflammatory cytokines [71]. These changes are likely due to the altered hormonal and cytokine milieu present in the elderly and may contribute to an increased incidence of inflammatory diseases [73].

The mucosal immune system is not spared from senescence. Mucosal-associated lymphoid tissue (MALT) becomes scarcer with age, with reduced lymphoid follicle development and associated antibody production. These changes determine a decreased intestinal barrier function as the levels of IgA, an immunoglobulin involved in mediating host-microbiome interactions, drop with MALT depletion.

'Inflammaging' refers to a chronic low grade inflammation present in elderly individuals due to dysregulated release of cytokines into the bloodstream [35]. In fact, the balance between pro- and anti-inflammatory cytokines can be used to determine a patient's risk profile for frailty and

mortality [74]. This process together with changes in the microbiota associated with aging may affect the clinical course of IBD due to abnormal immune responses and decreased mucosal tolerance.

Though changes in the immune system with age are well established, how these changes impact IBD and its phenotype through the age groups is still not known.

Therapeutic endpoints:

Treatment in IBD aims to achieve disease remission with both symptom resolution and mucosal healing [35]. Histologic resolution is not a target per recent consensus recommendations [75]. Biomarkers such as CRP and faecal calprotectin are to be used in the monitoring of IBD patients but are not targets for treatment in themselves. These recommendations apply to both long-standing and elderly onset IBD patients. However, the goal of remission can be unattainable in elderly patients not only due to their comorbidities but also compliance issues, polypharmacy and adverse reactions, among other limitations. This is especially true for deep mucosal healing which often requires a combination of immunosuppressants too aggressive for frail patients to tolerate. Therefore, tailoring treatment targets for elderly IBD patients may be necessary and can include simplification of treatment regiments with awareness of cost, mindfulness of potential drug interactions and strategies to improve quality of life which tackle particularly distressing symptoms such as incontinence, frequent stooling and pain [66].

Medical therapy:

Medication prescription patterns vary between younger and elderly IBD patients as the perceived limitations of the latter population group influence the clinician's decision. Several studies have demonstrated that sulfasalazine and corticosteroids are the most commonly prescribed medication classes in the elderly patient, with the biological and immunomodulators being prescribed significantly less frequently [8] [76]. Reasons for this could be due to the perceived milder disease course of elderly onset IBD and hence lesser need for strong immunosuppressant medication and the increased concern over adverse effects of the more aggressive medications in the older patients [77].

The choice of treatment depends on factors such as disease severity, location, extension, response to previous treatment schemes, comorbidity, use of concurrent medications and patient compliance. 5-Aminosalicylates are generally taken to be safe and effective medications for the treatment of mild to moderate UC while for Crohn´s disease their action remains

equivocal [78]. Despite this, 5-ASA use is widespread among elderly CD patients probably due to its favourable side effect profile [6]. All forms of these medications seem to be equally effective but it is important to consider that the elderly patient may lack the dexterity to correctly perform enemas or apply suppositories and situations of incontinence reduce the effectiveness of these methods. Oral dosing regimens should be simplified to once-daily prescriptions which have been proven to be of similar efficacy to split-dosing regimens [79]. 5-ASA nephrotoxicity has been reported in the literature [80] and though there is little evidence evaluating the use of these drugs in renal-impaired patients, caution is recommended when prescribing for this population group.

Corticosteroids are used not only in remission induction but also as long term maintenance therapy in the elderly population group despite the known corticosteroid complications [81]. Of note, elderly-onset IBD patients receive higher and more frequent doses of corticosteroids at diagnosis than patients who were diagnosed at a younger age [60]. Continual treatment with corticosteroids without an exit strategy can lead to increased mortality in IBD patients [82] and therefore chronicity should be avoided. Budesonide has a more favourable side effect profile than other glucocorticoids due to localized drug delivery and a high first pass metabolism which reduce systemic bioavailability [83]. Therefore, it is commonly used as induction therapy in patients with mild to moderate ileal or ileocecal disease [84]. However, budesonide has been linked to endocrine disturbances such as Cushingoid features and hypokalaemia as well as dyspepsia, behavioural changes, cutaneous reactions, menstrual changes and palpitations [85] which, though less common than for other glucocorticoids, are significantly more so than with placebo. As with other medications, corticosteroid clearance is decreased in older patients which increases the risk of drug interactions. Phenytoin, rifampicin, phenobarbital and ephedrine are inducers of cytochrome enzymes and therefore decreased the systemic levels of corticosteroids while inhibitors of these enzymes produce the opposite effect [86]. This pharmacological class is known to cause both dependency and tolerance which increase the need for immunosuppressant therapy. Corticosteroid dependence is particularly common in elderly individuals who are in themselves vulnerable to the complications of immunosuppression hence reinforcing the need for steroid-sparing strategies in maintenance regimens.

Among the many immunomodulator drugs in existence, azathioprine (AZA), 6-mercaptopurine (6-MP) and methotrexate (MTX) are the three most commonly used in the treatment of IBD. The thiopurines AZA and 6-MP are effective for induction and maintenance of remission and

no difference has been found in terms of efficacy and toxicity of these agents between elderly and younger IBD patients [15]. Among the side effects of thiopurines are idiosyncratic reactions such as rash, pancreatic and hepatitis and dose-dependent myelotoxicity and hepatotoxicity. In prevention of the latter two effects, regular monitoring with a full blood count and liver profile are essential. Allopurinol has an interesting effect over thiopurine metabolism. It not only inhibits xanthine oxidase and therefore interferes with a thiopurine catabolism pathway mediated by this enzyme [87] but also in patients who preferentially metabolise 6-MP to methyl mercaptopurine, allopurinol can be used to circumvent this hypermethylation pathway and therefore reduce drug toxicity. However, this potentially beneficial effect is offset by the findings of infectious complications in elderly IBD patients treated concomitantly with immunomodulators and allopurinol [88]. Methotrexate can be used for induction and/or maintenance therapy for CD in patients intolerant to AZA or 6-MP or who are steroid dependent or refractory. Known adverse effects include bone marrow suppression, hepatic fibrosis, alopecia and gastrointestinal toxicity. MTX has renal excretion and therefore age-related changes in kidney function must be investigated before prescribing this drug to an elderly IBD patient. It is important to note that NSAID´s and penicillin interact with MTX by reducing its excretion and therefore increasing toxicity.

Anti-TNF agents, also called biological agents, are used in the treatment of moderate to severe UC and CD, both in induction and maintenance of corticosteroid-free remission. Studies have shown that an earlier initiation of these agents, with their potential for mucosal healing, can improve outcomes for IBD patients both in the short and in the long-term [89] [90]. These findings support a top-down approach in treatment management as opposed to the conventional step-up currently in practice. However, though the former approach is being employed by many gastroenterologists in the treatment of younger patients, recent evidence demonstrates underuse of biologicals and immunomodulators in the elderly population, with preference for 5-ASA and corticosteroid prescription and hence a bottom-up approach [6] [60] [76]. Reasons for this include concerns about the safety and efficacy of the stronger immunosuppressant agents in the older IBD cohort, especially the risk for infectious complications, drug interactions and malignancy. Though still sparse, the data from past trials seems to suggest that biologicals are effective to use in older patients [91]. However, the data also suggests an increased risk of infection and mortality when compared to the younger patients or patients of the same age group who did not receive biologicals [92] [93]. At present, the prescription of biologicals for an elderly IBD patient must be tailored to their clinical picture in that the benefit obtained from

disease activity control must outweigh the risks associated with this therapy, which may be greater in this age group.

Antibiotics are utilized as adjuncts to medical therapy in IBD patients. In situations of pouchitis, fistulizing CD, CD-related abscesses and fulminant colitis, metronidazole and ciprofloxacin are frequently used. Metronidazole has several adverse effects which include neuropathy, metallic taste and nausea [22] [94], all three of which are more common in the elderly patient. Moreover, its inhibitory effect over cytochrome enzymes increases the bioavailability of drugs such as calcium channel blockers, simvastatin and sildenafil [94]. Other side effects include increased lithium toxicity, potentiation of warfarin action with prolonged INR and disulfiram reaction when taken with alcohol. Ciprofloxacin has several drug-to-drug interactions due to its inhibitory influence over cytochrome enzymes [95]. It decreases theophylline clearance, increases warfarin levels and as a fluoroquinolone has the potential to increase the QTc interval.

Surgical therapy:

Surgical therapy is usually reserved for cases where medical treatment has failed or complications such as obstruction, fistulisation, abscess formation, toxic megacolon and intractable bleeding occur. For CD, there appears to be a decreased need for surgery in the elderly-onset IBD population group [96]. Risk factors for surgery in elderly patients include ileocolonic disease as well as structuring and penetrating disease behaviour [6]. Recurrence rates of CD after bowel resection are disparate between studies, ranging from a five-fold increase in risk in elderly patients to equal rates between age groups [97] [64] . One study demonstrated lower recurrence rates for elderly patients with CD although the time for recurrence was shorter than for younger patients (3.7 vs. 5.8 years) [98]. Overall, the prognosis of elderly-onset CD appears to be more favourable probably because the disease phenotypes more common in this age group are those associated with decreased risk of disease recurrence, namely less small bowel involvement and decreased penetrating disease. There is a lack of evidence regarding prophylaxis of recurrence in the elderly population and therefore recommendations on this matter are lacking.

For UC, surgical treatment is curative and is commonly performed in cases of colonic dysplasia or medically refractory disease. As in CD, elderly UC patients were less likely to undergo surgery compared to younger UC patients [99]. At time of diagnosis there was no significant difference in the requirement for colectomy between early and late-onset UC patients [100]. Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the preferred surgical technique

for most patients. This procedure is usually performed in two steps, firstly total colectomy with pouch formation and diverting ileostomy followed by ileostomy reversal 6 to 12 weeks later. A permanent end ileostomy is also an option for patients where IPAA is not recommended. The decision between surgical treatment or intensification of medical therapy in an elderly patient is influenced by the fact that age is an important risk factor for postoperative morbidity and mortality. Apart from advanced age, hypoalbuminemia and male gender are also considered predictors of poor surgical outcome in IBD patients [60]. A recent study analysing the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) dataset demonstrated that the elderly had a 5- to 10-fold increase in 30-day mortality after IBD-related surgery compared with young patients [101]. These results highlight the need for pre-operative management of comorbidities and patient optimization followed by scrupulous postoperative monitoring. Several studies comparing surgical techniques in younger and elderly patients have shown similar complication rates between these age groups. One retrospective cohort study compared small bowel resection, total and partial colectomy, laparoscopic total and partial colectomy and stricturoplasty and found no statistically significant increase in complication rates in older patients. Proctocolectomy with IPAA compared to proctocolectomy with ileostomy has similar surgical morbidity in younger and older IBD patients such that at present, the consensus is that age is not in itself an exclusion criterion for IPAA [102] [103] [104]. Functional outcomes after pouch surgery are in general encouraging in elderly patients though there appears to be a greater incidence of diurnal incontinence and nocturnal leakage among patients aged >65 [15]. Despite this fact, 89% of elderly UC patients stated that they would undergo IPAA again and 96% would recommend the surgery to others [102]. Therefore, the decision between IPAA and ileostomy must rely on careful patient selection with good anal sphincter function and adequate cognition being crucial for pouch success [7] [104].

Nutrition:

The link between diet and onset and/or exacerbation of inflammatory bowel disease has been studied extensively. Conclusions regarding prevention strategies include encouraging diets rich in fruits, vegetables and n-3 fatty acids and low in n-6 fatty acids, with less importance placed on the carbohydrate content of the diet [105]. Micronutrients remain a topic of considerable debate as randomized clinical trials which evaluate their influence in IBD prevention and remission are lacking. So far, the evidence available points to beneficial effects of vitamin D and zinc in the prevention of CD but not UC [106] [107].

The understanding that prevails in the scientific community is that there is no IBD diet that can promote remission of active disease. During disease flares the recommended nutritional plan should be adapted to the patient's clinical condition taking into consideration the capacity for oral intake, the absorptive capacity of the GI tract, specific nutritional deficits detected and therapeutic goals (supportive care, treatment of malnutrition or induction and maintenance of remission) [105].

IBD patients are at considerable risk of malnutrition as the disease process undermines normal nutrient absorption. CD poses a higher risk than UC because it can involve any part of the gastrointestinal system whereas UC is localized to the colon. Estimates suggest that 65-75% of CD and 18-62% of UC patients suffer from malnutrition [108]. The elderly are in themselves at increased risk of malnutrition due to a combination of physiological, social and economic factors. A mnemonic consisting of 9 D's is frequently used to aid in the identification of risk factors: dementia, dysgeusia, dysphagia, diarrhoea, depression, disease, poor dentition, dysfunction, and drugs [109]. As practitioners charged with the holistic care of elderly IBD patients, we must actively search for possible nutritional deficits and liaise with dietitians to improve nutritional therapy and avoid nutrition-related disorders.

Future perspectives:

Environmental factors:

The faecal microbiome and its dysregulation in inflammatory bowel disease are topics of active research. IBD results from a complex interplay of environmental, immunological and genetic factors. Part of the disease process is thought to stem from dysregulated immune system activation against commensal microbiomes with loss of tolerance to intestinal antigens and consequent gut inflammation. Improved DNA and RNA sequencing techniques have allowed the identification of the microbial composition of the gastrointestinal tract. Consequently, the correlation between changes in microbial diversity and pathological states such as IBD is now clear and therapies aimed at restoring eubiosis are in development.

Faecal microbiota transplantation involves the transfer of a suspension of liquid faeces from a healthy donor to a diseased recipient. Though it has proven to be very successful in the short-term management of recurrent Clostridium difficile infections its use in IBD is still under investigation. A recent systematic review of 18 studies where FMT was performed on IBD patients (9 cohort studies, 8 case reports and 1 RCT) demonstrated a 45% clinical remission rate post-transplantation (36.2% when excluding case series to reduce publication bias). In subgroup analysis, this value dropped to 22% in UC patients and 60.5% in CD [110]. Though there appears to be a more favourable response in CD, further studies are needed to support this. Furthermore, issues such as donor selection, means of administration (i.e. nasogastric or nasoduodenal tube, colonoscope, enema or capsule), timing and frequency (use during flares or as maintenance therapy, as a single dose therapy or multiple doses) as well as long-term safety remain to be answered [111]. Therefore, due to the emerging nature of FMT, there is still insufficient evidence to support the inclusion of FMT in the armamentarium of treatment options for IBD.

Probiotics are live, non-pathogenic organisms prescribed with the aim of restoring microbial balance in the GI tract. They are thought to act by lowering intestinal pH, inhibiting colonization and mucosal invasion by pathogenic microorganisms as well as regulating the immune response of the host. Probiotics containing Escherichia coli Nissle 1917 or VSL#3, have shown efficacy in patients with mild to moderate UC for the induction of remission [112] [113]. Despite these promising results, further studies are required to characterize effective strains, determine the appropriate dosage and frequency of administration as well as long-term safety. VSL#3 has also been demonstrated to decrease the onset of pouchitis [114] and therefore is now indicated for the prevention and maintenance of remission of this clinical entity.

Genetics:

The genetic contribution to elderly-onset IBD remains unclear. However, the lack of family history in elderly-onset IBD could imply that the influence of genes is greater in long-standing IBD than in the older subset [23]. Genome-wide association studies (GWAS) have so far contributed to identifying over 99 genetic risk loci, and understanding the biological pathways these loci mediate is crucial to comprehending IBD pathophysiology. The goal of creating a genetic risk profile panel that can be applied to clinical practice to determine a patient's probability of developing IBD or, if it is a patient with a diagnosis of IBD, a panel to determine the risk of developing severe disease, remains to be reached and further studies are needed before we can achieve it. Furthermore, it is known that genetic traits can be used to determine how a patient will respond to a specific treatment (e.g. 6-mercaptopurine response) [115]. Therefore, should this knowledge become applicable in practice, therapy can be truly personalized to the patient's sensitivity profile thereby reducing adverse effects and increasing efficacy.

Identifying a causal gene for IBD seems unlikely due to the complex interplay between environmental, genetic and microbial factors involved in the pathophysiology of the disease. However, through genetic models analysing defects arising from loci associated with IBD, new targets for diagnostics and directed gene therapy could arise [116].

Immunology:

Serological immune markers for CD include anti-Saccharomyces cerevisiae antibodies (ASCA) IgG, ASCA IgA, perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), anti-outer membrane porin of *Escherichia coli* (OmpC), pseudomonas anti-I2, flagellin (anti-Cbir1) and several glycans (chitobioside, laminariboside and mannobioside) [117]. For UC, there is fewer knowledge on the clinical utility of serum markers except for p-ANCA and anti-CBir1, which have been correlated with increased risk of pouchitis after colectomy [118]. There is no evidence validating the use of these markers in elderly-onset IBD and therefore investigation on the topic is needed.

The development of biomarkers is a crucial area of investigation. Research on metabolome biomarkers, which can typify microbiome activity, and proteomic technology for identification of biomarkers is ongoing [119]. Though at present their inclusion in clinical practice is not feasible, in the future, as the aetiology of IBD is clarified, the biomarkers discovered may be integrated into a molecular diagnostic and prognostic tool.

An interesting area of research within molecular drug design involves regulators of G-protein signalling proteins (RGS) and their role in modulating intestinal inflammation [120]. RGS have been implicated in the modulation of opioid, cannabinoid and serotonin G-protein response to extracellular stimuli. In the GI tract, they serve as a promising target to reduce the severity of IBD by curbing the immunological pathways involved in intestinal inflammation. Though still in its commencement, this research is opening the field for the discovery of novel anti-IBD drugs at a time when the increasing incidence of IBD coupled with the known issues of the pharmacotherapy available are of major concern [19].

Conclusion:

In the present work, evidence relating to the differences between elderly-onset and long-standing IBD have been expounded. From this, the question arises as to whether they may in fact represent two different diseases within the spectrum of inflammatory bowel disease, with differing pathophysiological pathways determining timing of occurrence. It seems unlikely that onset of disease is simply a random event because of the clinical heterogeneity present between age groups (if it were, one would expect a similar phenotype irrespective of age of onset). The body of evidence pointing to differing mechanisms at play across the ages is growing, with genetic, immunologic and environmental contributions to aetiology being analysed and determined. As of yet, the factors determining age of onset remain unknown. However, the continued study of immunosenescence and its influence on the intestinal microbiome in IBD disease models may elucidate on the aetiological mechanisms at play.

IBD in the elderly, be it long-standing or elderly-onset, presents many challenges to the caring physician. From differential diagnosis to treatment and long-term patient management, the older IBD patient differs from the young and requires a tailored approach with deviation from conventional practice algorithms. Only through cooperation between the primary health care network, specialist practitioners, the patient and his family will optimization of treatment efficacy and improvement in the quality of life of the elderly IBD-patient be possible.

Though the paradigm of step-up treatment is changing towards more aggressive disease control earlier on in disease presentation, this is far from being implemented in the older patient cohort from fear of comorbidities and adverse reactions. A clinical distinction of fit vs frail elderly may assist in the decision process in that the former should be granted access to newer therapies and not be excluded simply due to an age criterion.

The studies upon which current knowledge on IBD is based upon are, in general, of inferior levels of evidence. The elderly are a subpopulation that are all too often excluded from clinical trials, resulting in lack of evidence specific to this age group and thereby complicating the therapeutic decision making process. Therefore, further investigation is warranted to empower the creation of evidence-based guidelines for the management of this population group. An international multicentric effort is required to guarantee that the research being carried out is of the highest level of evidence and that the elderly are adequately included in clinical trials. Only in these conditions will the development of therapeutic guidelines adapted to the elderly patient be feasible.

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